MYOTONIC DYSTROPHY AND THE HEART

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Myotonic dystrophy (dystrophia myotonica, DM) is the most frequently inherited neuromuscular disease of adult life. DM is a multisystem disease with major cardiac involvement. Core features of myotonic dystrophy are myotonia, muscle weakness, cataract, and cardiac conduction abnormalities. Classical DM (first described by Steinert and called Steinert's disease or DM1) has been identified as an autosomal dominant disorder associated with the presence of an abnormal expansion of a CTG trinucleotide repeat on chromosome 19q13.3 (the DM 1 locus). A similar but less common disorder was later described as proximal myotonic myopathy, caused by alterations on a different gene on chromosome 3q21 (the DM2 locus). This article will mainly focus on DM1. It will provide an insight into the epidemiology and genetic alterations of the disease and provide up-to-date information on postmortem and clinical findings and on diagnostic and therapeutic options in patients presenting cardiac involvement.

EPIDEMIOLOGY AND CLASSIFICATION OF DM1

The incidence of DM1 is estimated to be 1 in 8000 births and its worldwide prevalence ranges from 2.1 to 14.3/100 000 inhabitants.[1] Based on the age of onset and on its clinical features, DM1 can be divided into three forms: congenital, classical, and minimal, which may occur in the same kindred.

Congenital DM1 presents at birth or during the first year of life in a severe form. It is characterised by neonatal hypotonia, facial diplegia, joint contractures, frequent and often fatal respiratory failure, feeding difficulties, and developmental delay. The risk of dying from congenital DM1 in the neonatal period is high.[1] Patients who survive exhibit non-progressive psychomotor retardation and may subsequently exhibit the features of the adult-type, classical form of DM1.

In the classical form, which is the most common, symptoms become evident between the second and the fourth decade of life, showing a slow progression over time (table 1). The key feature of the disease is myotonia, which is characterised by delayed relaxation after muscular contraction (fig 1A,B); progressive muscular weakness (dystrophy) and wasting are also typical findings; facial, axial, semi-distal, and distal compartments are predominantly involved. DM1 is, however, a multisystem disorder; indeed, affected patients can manifest abnormalities of other organs and systems including the eye (cataract), the endocrine system (diabetes, thyroid dysfunction, hypogonadism), the central nervous system (cognitive impairment, mental retardation, attention disorders), the gastrointestinal system (dysphagia, constipation, gallbladder stones, pseudo-obstruction), and the heart (table 2).

Minimal DM1 begins later in life, usually after 50 years of age, with a very mild degree of muscle weakness and myotonia or only cataracts, associated with a normal lifespan.

GENETIC ALTERATIONS OF DM1

DM1 is an autosomal dominant disorder with incomplete penetrance and variable phenotypic expression. The genetic basis of DM1 is known to include mutational expansion of a repetitive trinucleotide sequence (CTG) in the 3′-untranslated region of the DMPK gene (myotonic dystrophy protein kinase gene) on chromosome 19q13.3. While 5-34 CTG repeats are observed in normal alleles, their number may reach 50–2000 in DM1.[2] The process which leads from abnormal expansion of CTG repeats in a non-coding region of DMPK gene to cellular dysfunction is still incompletely understood. However, the localisation of DMPK in the heart muscle at the level of intercalated discs, combined with the observation that DMPK reduction in animal models compromise conduction both at the level of the atrioventricular node and of the His-Purkinje system,[3] suggest impairment of intercellular impulse propagation as a possible mechanism of disease.

Pathologic expansion of the CTG repeats is unstable both during mitotic and meiotic divisions. Mitotic instability explains the presence of somatic mosaicism, a common feature of DM1. Meiotic instability represents the mechanism underlying the phenomena of "anticipation" and "reverse mutation" observed during parent-to-child transmission in DM1 pedigrees. "Anticipation" occurs

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Table 1 Muscular manifestations of myotonic dystrophy (DM1)

Myotonia	▶ Active and evoked
Muscular dystrophy and wasting	▶ Facial and masticatory muscles (facies myotonica) ▶ Axial compartment ▶ Semidistal compartment ▶ Distal compartment ▶ Pharyngeal muscles (nasal speech, dysphagia) ▶ Respiratory muscles
Central nervous system	▶ Cognitive impairment ▶ Mental retardation ▶ Attentive disorders

Table 2 Systemic involvement in DM1

Eye	▶ Cataract
Endocrine system	▶ Diabetes ▶ Thyroid dysfunction ▶ Hypogonadism
Gastrointestinal tract	▶ Dysphagia ▶ Constipation ▶ Gallbladder stones ▶ Pseudo-obstruction
Central nervous system	▶ Cognitive impairment ▶ Mental retardation ▶ Attentive disorders
Heart	

in earlier onset and a greater severity of symptoms in succeeding generations is caused by a meiotic increase in the size of CTG repeats, while the less common "reverse mutation", possibly accounting for incomplete penetrance of DM1, is caused by a meiotic regression in the size of the expansion bringing the number of the CTG repeats towards normal range.[2]

Many attempts have been made to find a possible correlation between the number of CTG repeats and severity of clinical manifestations of DM1. Despite earlier controversial results, evidence is accumulating in favour of a correlation between cardiac involvement and CTG expansion.[2 4 5] Indeed, the number of CTG repeats seems on average to influence the timing of cardiac complications,[6] to predict the presence and the progression of ECG abnormalities,[5] and the risk of major cardiac events,[7] but it does not predict abnormal findings at electrophysiological study (EPS).[8] Analysis of CTG repeats is, however, of limited predictive value in individual patients because of the overlap between expansion sizes seen in different phenotypic groups, somatic mosaicism, and current analysis of CTG repeats from peripheral blood leucocyte DNA instead of skeletal and cardiac muscle DNA.[2]

CARDIAC INVOLVEMENT IN DM1

Pathology and mechanisms of cardiac death

Endomyocardial biopsies and postmortem studies performed on patients with DM1 have documented various degrees of non-specific changes, such as interstitial fibrosis, fatty infiltration, hypertrophy of myocardiocytes, and focal myocarditis. A selective and extensive impairment of the conduction system is the most common finding.[9]

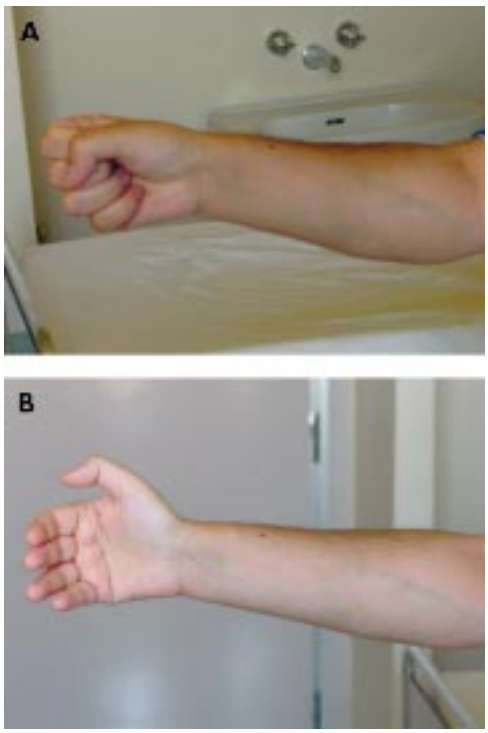

Figure 1 The grip test is a quick and easy way to determine the presence of active myotonia. After contraction of the fist (A) the patient is unable to relax the muscles of the hand (B). Photographs courtesy of Dr Gabriella Silvestri, Unione Italiana Lotta alla Distrofia Muscolare, Sezione Lazio, Italy.

During a 10 year follow up study of 367 DM1 patients,[1] mortality was 7.3 times higher than that in an age matched reference population, with a mean age at death of 53 years and a positive correlation between age at onset of DM1 and age of death. In this series, respiratory failure and cardiovascular disease were the most prevalent causes of death, accounting for about 40% and 30% of fatalities, respectively. Cardiac mortality occurred because of progressive left ventricular dysfunction, ischaemic heart disease, pulmonary embolism, or as a result of unexpected sudden death.[1] Relative contribution of sudden death ranges from about 2–30% in different published series, according to selection criteria. The hypothesis that cardiac arrhythmias may represent the most prevalent cause of sudden death in DM1 patients is supported by the absence of other causes of sudden death at necropsy studies. Sudden cardiac death may be caused by ventricular asystole, degeneration of ventricular tachycardia (VT), ventricular fibrillation (VF) or electromechanical dissociation. The consistent evidence of the degeneration of the conduction system in DM generated the hypothesis that bradyarrhythmias might represent the most prevalent mechanism of SD. However, ventricular tachyarrhythmias are increasingly recognised as a common finding in these patients (fig 2A,B), possibly explaining some cases of sudden death after pacemaker implant.

Clinical presentation

Heart disease is common in DM1 but its prevalence is difficult to estimate precisely, as different definitions have been used in the literature. Neuromuscular alterations are usually the initial clinical manifestation of DM1 (with or without subclinical cardiac involvement), but cardiac symptoms may be occasionally the first to appear. Cardiac involvement is characterised by conduction system abnormalities, supraventricular and ventricular arrhythmias and, less frequently,

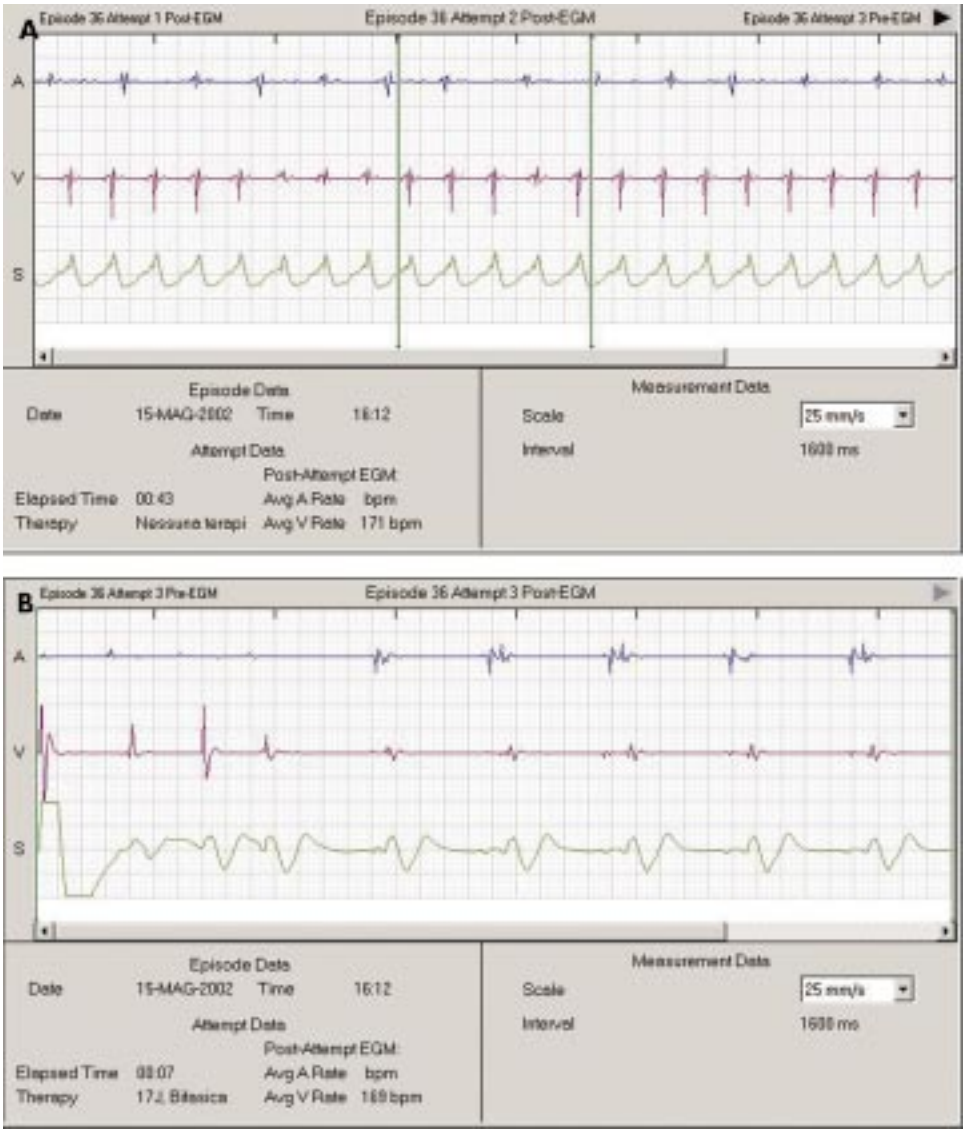

Figure 2 (A) Intracardiac electrograms (EGM) of a spontaneous episode of sustained ventricular tachycardia as recorded from the cardioverter-defibrillator (ICD) implanted in a 32 year old male patient affected by DM1. From top to bottom the tracings show the atrial EGM, the ventricular EGM, and a pseudo-surface lead II derived from signals recorded between the shock coils and the ICD. Atrioventricular dissociation, enabling a diagnosis of ventricular tachycardia, is evident. (B) Resumption of sinus rhythm after a 17 J biphasic DC shock.

myocardial dysfunction and ischaemic heart disease (table 3). At variance with other neuromuscular diseases, patients with DM1 rarely present overt clinical manifestations of cardiomyopathy ("myotonic" heart disease).[10]

Conduction system defects

Conduction system abnormalities are commonly observed in DM1. Any part of the conduction system may be affected, but the His-Purkinje system is most frequently involved. Minor conduction defects are often present in 12 lead ECG in asymptomatic DM1 patients in the early stages of disease; their progression towards more severe conduction defects may cause shortness of breath, dizziness, fainting, syncope, and sudden death. Rate of progression of conduction abnormalities is usually slow,[11] but fast progression has been occasionally observed thus making the clinical course of individual patients rather unpredictable. Delayed impulse propagation along the conduction system can be associated with a long PR interval (prevalence ranging from 20–40% in different studies, depending on patient selection criteria) and/or with a wide QRS complex (prevalence ranging from 5–25% in different studies, depending on patient selection criteria). Unfortunately, the presence of a long PR interval does not give any clue as to the site of the conduction delay, as it may occur at any level from the atrium to the His bundle, through the atrioventricular node. However, when a wide QRS is also present (for example, right or left bundle brunch block), the probability of an infrahissian (below the His bundle) conduction impairment is higher. Of note, prolongation of the HV interval has been observed in about half of unselected patients with DM1.[9 12]

In patients with DM1, analysis of late potentials has unique implications. Late potentials are expression of delayed myocardial activation usually caused by abnormal tissue (for example, myocardial fibrosis or necrosis, as typically observed in ischaemic heart disease after myocardial infarction), and are considered predictors of ventricular arrhythmias. Delayed myocardial activation in DM1 is not a consequence of inhomogeneous conduction through scattered areas of fibrosis but rather of delayed activation along the His-Purkinje system.[13] In DM1, abnormal late potentials are thus an expression of a conduction defect, and represent an important non-invasive clue to the presence of a long HV interval. QRS duration $\geq$ 100 ms and low amplitude signals in the last 40 ms of QRS complex $\geq$ 36 ms can predict a prolonged HV interval at EPS with good sensitivity and specificity (80% and 83.3%, respectively).

Tachyarrhythmias

In DM1 patients, supraventricular tachyarrhythmias are a common finding on 12 lead ECG or during 24 hour Holter monitoring, and may be asymptomatic. Most common

Table 3 Cardiac involvement in DM1

Conduction system	▶ Atrioventricular block, any degree
Arrhythmias	▶ Supraventricular –atrial premature complexes –atrial tachycardia –atrial flutter –atrial fibrillation ▶ Ventricular –ventricular premature complexes –ventricular tachycardia –ventricular fibrillation
Ventricular function	▶ Systolic function impairment ▶ Diastolic function impairment
Ischaemic heart disease	
Mitral valve prolapse	

arrhythmias are atrial flutter or fibrillation, observed in up to 25% of patients both as unsustained and sustained forms. Atrial flutter, atrial fibrillation, and atrial tachycardia are also easily inducible at EPS even in the absence of previously documented spontaneous episodes, but the clinical implications of these findings are still uncertain.

Ventricular arrhythmias are frequent. Spontaneous episodes of both monomorphic and polymorphic VT and even VF have been consistently reported.[14] Therefore, in patients with clinical symptoms suggestive of ventricular tachycardia (for example, lipothymia, syncope) and/or with a family history of sudden death, an EPS is strongly advised.[7 8] The prognostic value of inducible VT in patients without a history of spontaneous VT and without symptoms suggestive of VT is still uncertain. In a seminal study on DM1 and cardiac disease, VT could be induced at EPS in 18% of patients referred for conduction abnormalities in the absence of ventricular arrhythmias during Holter monitoring.[8] Inducible VT is most commonly represented by unsustained polymorphic VT, but sustained polymorphic VT, VF, and both sustained and unsustained monomorphic VT have also been reported. Given the risk of sudden death in these patients, the prognostic significance of inducible VTs, even when polymorphic and unsustained, should be carefully considered, as risk stratification criteria used in other subsets of patients may not apply to DM.[15]

Mechanisms of monomorphic VT in DM are:

- re-entry around areas of fibro-fatty degeneration of the myocardium (possible)
- bundle brunch re-entry (typical)
- triggered activity.

In bundle branch re-entry ventricular tachycardia (BBRVT) the loop of the re-entrant circuit runs around the two ramifications of His bundle, which represent the anterograde and the retrograde limb (fig 3). Cardiac involvement in DM1 represents an ideal substrate for this type of re-entry, due to the common presence of a delayed conduction along the His bundle branch (prolonged HV interval) which is essential for BBRVT to occur.[16] Identification of bundle branch re-entry VT is important because it can be cured by radiofrequency ablation of one of the two limbs of the circuit. BBRVT is not easily inducible by standard programmed ventricular stimulation, while it is induced by short-long-short sequences which should be performed during the assessment of DM1 patients.[16] VT originating from the left posterior fascicle of His bundle (with characteristic RBBB and superior axis appearance on 12 lead ECG), which can be cured by radiofrequency ablation, has also been reported in these patients.

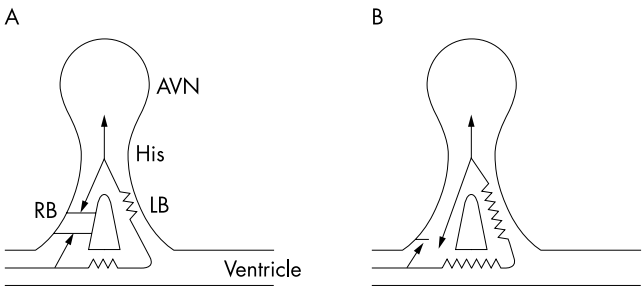

Figure 3 Bundle branch re-entry. (A) A ventricular premature impulse is blocked retrogradely in the right bundle branch (RB); conduction proceeds retrogradely through the left bundle branch (LB) up to the His bundle (His); from the His bundle, the impulse travels anterogradely over the right bundle branch which is still refractory, thus blocking propagation. (B) Conversely, if the right bundle branch has enough time to recover, the impulse can be conducted anterogradely to the ventricles, then retrogradely through the left bundle branch up to the His bundle, thus maintaining a macro-reentry. AVN, atrioventricular node.

Myocardial dysfunction, ischaemia, and other features of cardiac involvement

Overt myocardial dysfunction (myotonic heart disease) is not frequent. However, subclinical, mild myocardial dysfunction may be detected. Symptoms of heart failure are infrequent because of the limited level of activity of these patients and of their difficulties in reporting symptoms caused by mental retardation. The existence of a myocardial equivalent of skeletal muscle myotonia (myocardial myotonia) has been confirmed by assessment of diastolic function by echo Doppler parameters.[17] Ischaemic heart disease is sometimes observed as chronic stable angina, unstable angina, and acute myocardial infarction. Microvascular dysfunction has also been described in DM1 patients suffering from chest pain, exhibiting a positive thallium scan and normal coronary arteries.[18] Mitral valve prolapse has been reported in 25–40% of most DM1 series.[9] Hypertrophic cardiomyopathy and left ventricular hypertrabeculation have been described in case reports.

Management of cardiac involvement in DM

A careful cardiac evaluation including basal ECG, 24 hour Holter monitoring, echocardiogram, and signal averaged ECG should be routinely performed in all patients presenting with DM1. A history of fainting, palpitation, shortness of breath, lipothymia, and syncope should be carefully searched by interviewing not only the patient but also his or her relatives. Indications for EPS in DM1 patients are still debated but, given the risk of sudden death, we suggest an early invasive approach in selected subsets of patients as summarised in table 4. When classical indications[19] are met, pacemaker implant is needed and should not be delayed. Asymptomatic AV conduction delay, in particular in the presence of a prolonged HV interval, represents one of the major therapeutic challenges in DM1, as data on the rate of progression to complete atrioventricular block are conflicting. Which degree of HV interval prolongation should be considered an indication for prophylactic pacing in the absence of clinically relevant bradyarrhythmias is still an open issue. Recent findings, however, suggest that a prolongation of HV interval beyond 70 ms may warrant a prophylactic pacemaker implant even in the absence of symptoms.[20]

Treatment of ventricular arrhythmias is also an area of considerable debate. When classical criteria are met,[19] an implantable cardioverter-defibrillator should be implanted without

Table 4 Suggested indications for electrophysiological study in DM1 patients

Disturbances and/or symptoms suggestive of arrhythmias	Syncope, lipothymia, dizziness, palpitations
Family history	Sudden death Ventricular fibrillation Sustained VT Pacemaker implant
Non-invasive findings suggestive of intra- or infrahissian AV conduction disturbances (with or without symptoms)	LBBB RBBB + LAFH RBBB + LPFH
	First degree AV block with: PR interval >240 ms LAFH LPFH
	Second or third degree AV block
	Signal averaged ECG positive for late potentials
Sinus node dysfunction (with or without symptoms)	Sinus pause >3 seconds Sinus bradycardia <40/min
Ventricular arrhythmias (with or without symptoms)	Frequent ventricular premature beats Non-sustained VT Sustained VT

AV, atrioventricular; LAFH, left anterior fascicular hemiblock; LBBB, left bundle branch block; LFPH, left posterior fascicular hemiblock; RBBB, right bundle branch block; VT, ventricular tachycardia.

Myotonic dystrophy and cardiac involvement: key points

- Cardiac involvement is mainly represented by conduction abnormalities at ECG
- Conduction abnormalities are progressive, but the rate of progression is not clear
- Ventricular arrhythmias are common
- The unusual bundle branch re-entry ventricular tachycardia should be actively sought as radiofrequency ablation may be curative
- Sudden death represents 2–30% of fatalities in patients with DM1. Possible mechanisms are ventricular asystole, degeneration of ventricular tachycardia, ventricular fibrillation or electromechanical dissociation. The respective prevalence of these mechanisms is unknown
- Overt myocardial dysfunction is rare; however, impairment of ventricular systolic and diastolic functions may be part of the cardiac scenario

delay. A major effort is needed for identification of BBRVT which can be cured by radiofrequency ablation alone. When a VT is induced in an asymptomatic patient, the appropriate treatment strategy is as yet undetermined.

CONCLUSION

Conduction system abnormalities, arrhythmias and, less commonly, myocardial dysfunction and angina are observed in patients with DM1 and may occasionally represent the initial manifestations of disease, even in the absence of overt neuromuscular involvement. Thus, cardiologists should be aware of this diagnosis. Conversely, in all patients presenting with DM1 a careful clinical and diagnostic evaluation needs to be performed for the identification of patients at risk of major cardiac events. An attitude of a low threshold for invasive procedures is suggested, considering the unclear rate of cardiac disease progression and the risk of sudden death in some subsets of patients (table 4). Several questions are still unanswered. Future studies are needed in order to improve the identification of patients at risk of sudden death. A prospective, long term multicentre study (RAMYD, risk of arrhythmia in myotonic dystrophy) is now ongoing which will hopefully contribute to the formulation of evidence based guidelines for the management of cardiac conditions associated with DM1.

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